PCT/GB03/002601

Rec'd PCT/PTO 16 DEC 2004

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 20 AUG 2003
WIPO PCT

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed P. Mahoney

Dated 10 July 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
L
- 3 DEC 2002
NEWPORT

The Patent Office

10/77

03DEC02 E767998-1 010057
P01/7700 0.00-0228111.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 00303GB-1

2. Patent application number *(The Patent Office will fill in this part)* — 0228111.1

03 DEC 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Norton Healthcare Limited
Ivax Quays
Albert Basin
Royal Docks
LONDON E16 2QT
GB

Patents ADP number *(if you know it)* 06188221004

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of invention — PHARMACEUTICAL COMPOSITION

5. Name of your agent *(if you have one)* — MARTIN ALEXANDER HAY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

13 QUEEN VICTORIA STREET
MACCLESFIELD
CHESHIRE
SK11 6LP

Patents ADP number *(if you know it)* 08078438001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body
See note (d))

No

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	14
Claim(s)	3 DM
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application

Signature [signature] Date: 02 Dec 02

12. Name and daytime telephone number of person to contact in the United Kingdom

MARTIN A. HAY 01625 500057

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write you answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

Pharmaceutical Composition

The present invention relates to a pharmaceutical composition. More particularly, it relates to an aerosol composition comprising a cannabinoid, to a metered dose dispenser containing the composition and to a method of administering the composition to a patient.

Cannabis is known to be useful in therapy, for example in the treatment of nausea and vomiting associated with cancer chemotherapy, anorexia associated with AIDS, pain, epilepsy, glaucoma, asthma and mood disorders. The principle active ingredient in cannabis is delta-9-tetrahydrocannabinol (delta-9-THC). A derivative of delta-9-THC, which possesses similar properties, is delta-8-tetrahydrocannabinol (delta-8-THC). Collectively, cannabis, delta-9-THC and derivatives thereof, such as delta-8-THC, are known as cannabinoids.

International patent application publication number WO 01/66089 and United States patent application publication number 2002/0031480 disclose aerosol compositions comprising a cannabinoid and a propellant for administration to patients using a metered dose dispenser.

It is reported in WO 01/66089 that administration of aerosol compositions comprising the cannabinoid, delta-9-THC, and a propellant to the lungs of patients caused the patients to cough. Applicant has encountered a similar problem when administering aerosol formulations comprising delta-8-THC. This cough reaction is undesirable, because it results in exhalation of much of the inhaled dose.

Surprisingly, it has now been found that by incorporating a sufficient amount of a certain kind of ingredient into the aerosol compositions, the cough reaction of patients is suppressed.

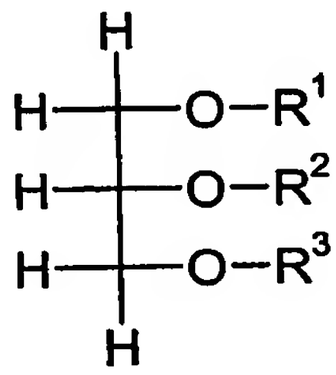
According to one aspect, therefore, the present invention provides a pharmaceutical composition for administration as an

aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.

Particularly good results have been obtained by incorporating medium chain triglycerides and propylene glycol diesters in a weight ratio of triglyceride to cannabinoid of at least 2:1, with the best results being obtained using weight ratios of at least 3:1 together with ethanol as a co-solvent.

According to a preferred aspect, therefore the cough suppressant is a medium chain triglyceride or propylene glycol diester.

Medium chain triglycerides are well known in the pharmaceutical formulation art, where they are mainly used in oral, parenteral and topical formulations. They are generally commercially available as mixtures of triglycerides of fatty acids consisting predominantly of octanoic (caprylic) and decanoic (capric) acid and may thus be represented by the general formula

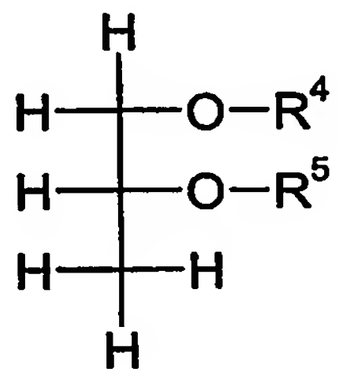


in which each of R^1, R^2 and R^3 independently represents a group of formula $-CO-(CH_2)_n-CH_3$ in which n is an integer of from 6 to 8.

Examples of commercially available medium chain triglycerides are MIGLYOL™ 810 and 812, both caprylic/capric triglycerides available from CONDEA Chemie GmbH, Oleochemicals, Arthur-Imhausen-Str. 92, D-58433 Witten, Germany or CONDEA Vista Co., Commerce Dr., Cranford, NJ 07016, United States, and CRODAMOL™ GTCC or CRODAMOL™ PC DAB 10(S), both caprylic/capric triglycerides, available from Croda

Chemicals Ltd., Rawcliffe Bridge, Goole, East Riding, DN14 8PN.

Medium chain diesters of propylene glycol are generally commercially available as mixtures of diesters of fatty acids consisting predominantly of octanoic (caprylic) and decanoic (capric) acid and may thus be represented by the general formula



in which each of R^4 and R^5 independently represents a group of formula $-CO-(CH_2)_n-CH_3$ in which n is an integer of from 6 to 8.

An example of a commercially available medium chain diester of propylene glycol is MIGLYOL™ 840, a propylene glycol dicaprylate/dicaprate, available from CONDEA Chemie GmbH, Oleochemicals, Arthur-Imhausen-Str. 92, D-58433 Witten, Germany or CONDEA Vista Co., Commerce Dr., Cranford, NJ 07016, United States.

The cough suppressant may conveniently be present in a weight ratio of cough suppressant to cannabinoid of from 2:1 to 25:1, preferably 2.5:1 to 15:1, most preferably 3:1 to 10:1.

The cannabinoid may be, for example, an extract of natural cannabis, delta-9-THC, a derivative of delta-9-THC such as delta-8-THC, cannabidiol, or a mixture of any of these. Preferably it is delta-8-THC.

The propellant may be, for example, an alkane, such as butane, or a fluorocarbon, such as 1,1,1,2-tetrafluoroethane (P-134a) or 1,1,1,2,3,3,3-heptafluoropropane (P-227). Preferably it is P-134a.

The weight ratio of propellant to cannabinoid in the composition is conveniently in the range of from 10:1 to 10,000:1, such as from 250:1 to 10,000:1, preferably from 50:1 to 500:1.

The composition may further comprise one or more solid or liquid carriers or excipients, such as a pharmaceutically acceptable solvent, for example an alcohol such as ethanol, an essential oil, such as peppermint, or a major component thereof, such as menthol, or a solid bulking agent, such as lactose. Preferably, the composition is a solution.

The one or more carriers or excipients in the aerosol composition may conveniently comprise from 0 to 25 % by weight of the total composition.

It has been found to be advantageous to include ethanol in the composition. The ethanol may make up from 0.1% to 25% by weight of the formulation, preferably 1% to 25% of the formulation, more preferably 1% to 15%, most preferably from 3 to 5%. It has been found that when using high levels of ethanol, for example from 15 to 25% by weight, it is possible to use a lower ratio of cough suppressant to cannabinoid than is effective with low levels of ethanol. Furthermore, with high levels of ethanol, certain pharmaceutically acceptable aerosol surfactants, such as isopropyl myristate and Brij 30 (a lauryl polyoxyethylene ether), can function as cough suppressants. However, the best results have been obtained using medium chain triglycerides and propylene glycol diesters in compositions containing from 3 to 5% by weight ethanol.

In certain cases, administration of the cannabinoid has been found to be associated with undesirable after effects, such as a burning or tingling sensation in the throat, or a dry throat. It has been found that these effects may be reduced or eliminated by incorporating an essential oil in the composition. Examples of essential oils include peppermint (of which the major constituent is menthol), eucalyptus (of

which the major constituent is cineole), aniseed and cajeput. According to a preferred aspect, therefore, the composition according to the present invention may further comprise an essential oil, such as peppermint, eucalyptus, aniseed or cajeput, or a major component thereof, such as methanol or cineole. Particularly good results have been obtained by incorporating menthol in compositions. The essential oil (e.g. menthol) preferably comprises from 0.02 to 0.1% by weight of the composition. The weight ratio of essential oil to delta-8-THC is preferably in the range of from 0.05:1 to 0.4:1, more preferably 0.1:1 to 0.3:1.

The pharmaceutical composition according to the invention may conveniently be administered to a patient using a metered dose dispenser, such as a metered dose inhaler. According to another aspect, therefore, the present invention provides a metered dose dispenser containing a pharmaceutical composition according to the invention. Preferably the metered dose dispenser is adapted to provide a unit dose containing from 0.05 to 0.5 mg of the cannabinoid, preferably from 0.1 to 0.2 mg.

According to another aspect, the present invention provides a method of administering an aerosol composition comprising a cannabinoid and a propellant to a patient, which comprises administering the cannabinoid and propellant with an effective amount of a cough suppressant.

According to another aspect, the present invention provides the use of an effective amount of a cough suppressant in the manufacture of a medicament for suppressing coughing when an aerosol composition comprising a cannabinoid and a propellant is administered to a patient.

As used herein, the term patient refers to any human or non-human animal. Preferably the patient is a human.

The aerosol composition is conveniently administered by inhalation. However, it may be administered via a pulmonary,

sub-lingual, nasal or buccal route. Thus, although the risk of provoking a cough is lower if an aerosol lacking a cough suppressant is administered via a sub-lingual, nasal or buccal route, it would be advantageous for patients to receive cannabinoid with a cough suppressant, in accordance with the present invention.

The following Examples illustrate the invention.

Example 1

Ingredient	Weight in mg
delta-8-THC	5.2 (0.1 mg dose)
P-134a	1606
Crodamol GTCC	15.9 (3.1:1 cough suppressant:cannabinoid)
Ethanol	42.7 (2.6% by weight)

Comparison Example 1

Ingredient	Weight in mg
delta-8-THC	6.1 (0.12 mg)
P-134a	1477
Crodamol GTCC	11.4 (1.9:1)
Ethanol	50.1 (3.3%)

Notes: A comparison between Example 1 and Comparison Example 1 shows that having a sufficient amount of Crodamol GTCC in the aerosol composition is important.

Example 2

Ingredient	Weight in mg
delta-8-THC	5.0 (0.12 mg)
P-134a	1220
Crodamol PC DAB 10(S)	52 (10.4:1)
Ethanol	0 (0%)

Example 3

Ingredient	Weight in mg
delta-8-THC	5.0 (0.23 mg)
P-134a	656
Crodamol PC DAB 10(S)	15.5 (3.1:1)
Ethanol	49 (7%)

Example 4

Ingredient	Weight in mg
delta-8-THC	5.1 (0.12 mg)
P-134a	1288
Crodamol PC DAB 10(S)	15.1 (3:1)
Ethanol	100 (7.2%)

Example 5

Ingredient	Weight in mg
delta-8-THC	5.1 (0.12 mg)
P-134a	1274
Crodamol PC DAB 10(S)	15.2 (3:1)
Ethanol	45.9 (3.5%)

Example 6

Ingredient	Weight in mg
delta-8-THC	5.2 (0.12 mg)
P-134a	1301
Crodamol PC DAB 10(S)	16.8 (3.2:1)
Ethanol	144.3 (10%)

Example 7

Ingredient	Weight in mg
delta-8-THC	6 (0.15 mg)
P-134a	1128
Crodamol PC DAB 10(S)	51 (8.5:1)
Ethanol	64 (5.4%)

Example 8

Ingredient	Weight in mg
delta-8-THC	10 (0.52 mg)
P-134a	581
Crodamol PC DAB 10(S)	105 (10.5:1)
Ethanol	0 (0%)

Example 9

Ingredient	Weight in mg
delta-8-THC	20 (0.22 mg)
P-134a	2689
Crodamol PC DAB 10(S)	300 (15:1)
Ethanol	0 (0%)

Comparison Example 2

Ingredient	Weight in mg
delta-8-THC	5 (0.24 mg)
P-134a	634
Crodamol PC DAB 10(S)	5.5 (1.1:1)
Ethanol	49 (7.2%)

Comparison Example 3

Ingredient	Weight in mg
delta-8-THC	5.5 (0.13 mg)
P-134a	1253
Crodamol PC DAB 10(S)	13.5 (2.5:1)
Ethanol	101 (7.5%)

Example 10

Ingredient	Weight in mg
delta-8-THC	10 (0.19 mg)
P-134a	1340
Crodamol PC DAB 10(S)	58 (6.8:1)
Ethanol	151 (10.1%)
Micronized lactose	10

Example 11

Ingredient	Weight in mg
delta-8-THC	5.1 (0.12 mg)
P-134a	1239
Miglyol 810	17.7 (3.5:1)
Ethanol	49.2 (3.8%)

Example 12

Ingredient	Weight in mg
delta-8-THC	5.4 (0.09 mg)
P-134a	1796
Miglyol 812	18 (3.3:1)
Ethanol	41.1 (2.2%)

Example 13

Ingredient	Weight in mg
delta-8-THC	10 (0.09 mg)
P-134a	3207
Miglyol 812	20.8 (2.1:1)
Ethanol	193.4 (5.7%)

Example 14

Ingredient	Weight in mg
delta-8-THC	10 (0.1 mg)
P-134a	3062
Miglyol 812	20.3 (2:1)
Ethanol	261.5 (7.9%)

Comparison Example 4

Ingredient	Weight in mg
delta-8-THC	5.6 (0.09 mg)
P-134a	1788
Miglyol 812	12.3 (2.2:1)
Ethanol	41.9 (2.3%)

Comparison Example 5

Ingredient	Weight in mg
delta-8-THC	10.3 (0.1 mg)
P-134a	3019
Miglyol 840	20.8 (2:1)
Ethanol	124.7 (4%)

Notes: A comparison between Examples 13 and 14 and Comparison Examples 4 and 5 shows that increasing the percentage by weight of ethanol can compensate for a reduced cough suppressant/cannabinoid ratio.

Example 15

Ingredient	Weight in mg
delta-8-THC	25 (0.2 mg)
P-134a	3451
Miglyol 812	75 (3:1)
Ethanol	145 (4%)

Example 16

Ingredient	Weight in mg
delta-8-THC	52.4 (0.2 mg)
P-134a	6952
Miglyol 812	132.4 (2.5:1)
Ethanol	597.9 (7.9%)

Example 17

Ingredient	Weight in mg
delta-8-THC	6.6 (0.14 mg)
P-134a	1423
Miglyol 840	17.1 (2.6:1)
Ethanol	48.6 (3.3%)

Comparison Example 6

Ingredient	Weight in mg
delta-8-THC	4.97 (0.1 mg)
P-134a	1137
Ethanol	274.2 (19.4%)

Example 18

Ingredient	Weight in mg
delta-8-THC	25.4 (0.20 mg)
P-134a	3568
Miglyol 840	77.8 (3.1:1)
Ethanol	146.18 (3.9%)
Eucalyptus Oil	2.7 (0.07%)

Example 19

Ingredient	Weight in mg
delta-8-THC	24.8 (0.20 mg)
P-134a	3509
Miglyol 840	78.4 (3.1:1)
Ethanol	148.35 (4.1%)
Peppermint Oil	2.7 (0.07%)

Example 20

Ingredient	Weight in mg
delta-8-THC	12.46 (0.10 mg)
P-134a	3500
Miglyol 840	44.2 (3.5:1)
Ethanol	145 (4.0%)
Menthol	1.3 (0.04%, menthol: delta 8 0.1:1)

Example 21

Ingredient	Weight in mg
delta-8-THC	5.0 (0.10 mg)
P-134a	1380
Miglyol 840	14.1 (2.8:1)
Ethanol	63.2 (4.4%)
Menthol	0.69 (0.05%, 0.14:1)

Example 22

Ingredient	Weight in mg
delta-8-THC	2.6 (0.04 mg)
P-134a	1861
Miglyol 840	7.53 (2.9:1)
Ethanol	62.7 (3.3%)
Menthol	0.36 (0.02%, 0.14:1)

Example 23

Ingredient	Weight in mg
delta-8-THC	2.62 (0.05 mg)
P-134a	1512
Miglyol 840	8.08 (3.1:1)
Ethanol	62.1 (3.9%)
Menthol	0.71 (0.04%, 0.27:1)

Example 24

Ingredient	Weight in mg
delta-8-THC	5 (0.11 mg)
P-134a	990
Brij™ 30	28 (5.5:1)
Ethanol	249 (20%)

Example 25

Ingredient	Weight in mg
delta-8-THC	6 (0.12 mg)
P-134a	1068
Isopropyl myristate	31 (5:1)
Ethanol	271 (20%)

The effect of administering the compositions of the Examples and Comparison Examples on patients was investigated as follows:-

The ingredients were filled in standard glass vials with a normal valve and seals. The completed units were put in a standard actuator and primed. Then one puff of each was taken in the normal manner by the volunteer.

The compositions of the Examples were found to produce no cough, whereas those of the Comparison Examples were found to produce a spontaneous cough within 2-3 seconds.

An experiment was also conducted to investigate whether the cough suppressant and cannabinoid could be administered sequentially. This is described below.

	First Dose	**Second Dose**
Ingredient	Weight in mg	Weight in mg
delta-8-THC	0	4.8 (0.01mg)
P-134a	1540.4	1502.0
Miglyol 812	25.2	
Ethanol	65.4 (4.1%)	62.3 (4.0%)
Eucalyptus Oil	0	18.6

The first dose, containing Miglyol 812, was inhaled twice, then the second dose was inhaled. The ratio of Miglyol 812: delta-8-THC inhaled was 10.5:1. A spontaneous cough was provoked after 5 seconds. This experiment shows that the cough suppressant needs to be administered with the cannabinoid.

Claims

1. A pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.

2. A composition as claimed in Claim 1, which is a solution.

3. A composition as claimed in Claim 1 or Claim 2, in which the weight ratio of cough suppressant to cannabinoid in the composition is in the range of from 2:1 to 25:1.

4. A composition as claimed in Claim 3, in which the weight ratio of cough suppressant to cannabinoid in the composition is in the range of from 2.5:1 to 15:1.

5. A composition as claimed in Claim 4, in which the weight ratio of cough suppressant to cannabinoid in the composition is in the range of from 3:1 to 10:1.

6. A composition as claimed in any one of Claims 1 to 5, in which the cough suppressant is a medium chain triglyceride or propylene glycol diester.

7. A composition as claimed in any one of Claims 1 to 6, in which the propellant is 1,1,1,2-tetrafluoroethane.

8. A composition as claimed in any one of Claims 1 to 7, in which the cannabinoid is delta-8-THC.

9. A composition as claimed in any one of Claims 1 to 8, which further comprises ethanol.

10. A composition as claimed in Claim 9, which comprises from 1 to 15% by weight of ethanol.

11. A composition as claimed in Claim 10, which comprises from 3 to 5% by weight of ethanol.

12. A composition as claimed in any one of Claims 1 to 11, which further comprises an essential oil or a major component thereof.

13. A composition as claimed in Claim 12, in which the essential oil or a major component thereof is menthol.

14. A composition as claimed in Claim 13, which comprises from 0.02 to 0.1% by weight of menthol.

15. A metered dose dispenser, which contains a pharmaceutical composition as claimed in any one of Claims 1 to 14.

16. A metered dose dispenser as claimed in Claim 16, which is a metered dose inhaler.

17. A metered dose dispenser as claimed in Claim 15 or Claim 16, which is adapted to provide a unit dose containing from 0.1 to 0.2 mg of cannabinoid.

18. The use of an effective amount of a cough suppressant in the manufacture of a medicament for suppressing coughing when an aerosol composition comprising a cannabinoid and a propellant is administered to a patient.

19. A method of administering an aerosol composition comprising a cannabinoid and a propellant to a patient, which

comprises administering the cannabinoid and propellant with an effective amount of a cough suppressant.

Abstract

A pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.